REMARKS

Status of the Claims:

Claims 36-45 are canceled without prejudice and without disclaimer.

Claims 46-65 are added.

Claims Objections:

Canceled Claims 36-45 were objected to for inaccuracy in designation of heat conductivity units. The new claims do not have this error.

Claim 40 contained a typing error. The objection is moot due to cancellation of claim 40.

Rejection of claims 40-44 and 45 under §112, Second Paragraph

Claims 40-44 were rejected for having an improper antecedent basis for the limitation "said solid surface".

The terminology "said" solid surface in claim 40 has not been repeated in the additional new claims; accordingly, this rejection is moot.

Rejection of claims 36 and 37 under 35 U.S.C. §102(b):

Claims 36 and 37 were rejected under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 5,780,295. The Action took the position that the methods claimed in the '295 patent are substantially the same as those in canceled claims 36 and 37 of the instant application because both the cited reference and the present invention appear to be generally directed to suspending a biological material in a cryoprotectant solution followed by spraying small droplets of the solution onto a very cold surface. The Action further did not distinguish use of stated smaller droplets in applicant's method, citing the '295 patent as disclosing an 8.2 microliter volume droplet, among other small sizes.

Applicants direct attention to added claims 46-53. The claims focus on the excellent results applicants have achieved with oocyte preservation; namely, a vitrified oocyte preparation that can be cultured after storage to yield viable specimens that can be impregnated and grown to at least the blastocyst stage. Exemplary results in Table 4 of the patent application show virtually

no effect from the vitrification process; *i.e.*, fresh oocytes did not exhibit better development or increased percent viability.

U.S. Patent 5,780,295 provides no guidance how to cryopreserve oocytes. At best, the entire patent specification is merely an invitation to experiment in discovering better methods of cell preservation. In fact, the specification specifically mentions red blood cells, mammalian cultured cells, platelets, leukocytes, Factor VIII, sperm, pancreatic islets, marrow cells, viruses and vaccines. In the experimental section, the only examples of cryopreserved vitrified biological materials are NCTC 929 cells, erythrocytes and polio virus (attenuated). Oocyte preservation is conspicuously missing from any examples and is not even mentioned in the discussion. It is well known in the art that oocytes are difficult to preserve and without guidance in the '295 patent there is no reason to believe that one of skill in the art would recognize that the disclosed methods would work, or if they could be achieved without undue experimentation.

On the fact that the '295 patent does not even mention oocytes, particularly in view of the known difficulties with oocyte preservation, applicants maintain that the '295 patent does not anticipate applicants' claimed method of oocyte cryopreservation. Additionally, Applicants' method is distinguishable from the generic method in the '295 patent. The claims in '295 are to a device. The sample preparation is set forth in the '295 examples. In general, samples were equilibrated, nebulized, frozen, dried and dehydrated. Nowhere does sample preparation involve quickly equilibrating, rinsing and then contacting microdrops of solution containing the oocytes and a cryoprotectant with a cold surface. Consequently, applicants method of preparing the samples is distinguishable from the methods disclosed and/or practiced in the '295 patent.

Rejection of canceled claims 40 and 41 under 35 U.S.C.§102(b):

Canceled claims 40 and 41 were rejected under 35 U.S.C.§102(b) as anticipated by U.S. Patent 5,780,295. The Action based rejection on the vitrification method disclosed in the '295 patent as applied to red blood cells or a mammalian cell line. Both cell types were used as examples of the method in the '295 patent. The Action argues that Applicants' concentration of cryoprotectant is within the range of any of the cryoprotectants listed in '295 and that the method

could be applied in exactly the same way (same steps) with oocytes as with the cells in the '295 patent.

As discussed above, Applicants' steps in sample preparation before contacting microdrops with a cryogenic surface, (regardless of surface shape, movement, or material) are not the same as employed in the '295 patent. The mere use of a cryoprotectant by Applicants does not give rise to anticipation from the general discussions presented in the '295 patent.

Accordingly, there is no basis for the Action to apply this rejection to the new claims.

Rejection of canceled claims 36-39 and 44 under 35 U.S.C. §103:

Canceled claims 36-39 and 44 were rejected under 35 §103(a) as unpatentable over U.S. Patent 5,780,295 taken with international application WO 99/66271. The Action admits that the '295 patent does not disclose anything about preserving oocytes or embryos; however, WO99/66271 refers not only to oocytes but also to a rapid freezing method by direct contact of microdroplets with a cold surface. The Action further takes notice that the WO document "...also teaches that cryopreservation agents are conventionally added to biological materials in order to reduce crystal formation and to maximize cell survival, that the optimal concentration of cryopreservation agents significantly increase cellular survival." Unfortunately, the Examiner's characterization of the WO document contradicts the actual teaching in the WO patent application. Taken alone, the quoted statement is misleading because the background section goes on to state that excessive concentrations of cryoprotectant may be toxic to cells and that several rather complex manipulations may be necessary to prevent toxicity. Moreover, in a general statement referring to previous reports of successful freezing and thawing performed on plant material, tissue culture cells, sperm and embryos, the observation is made that "...Oocytes, however, are particularly difficult to cryopreserve..."...A list of these difficulties is found beginning on line 26 and bridging over to line 26 on pages 4-5 of the WO application.

The WO publication emphasizes the difficulty in preserving oocytes, a problem also pointed out in Applicants' specification. The solution offered in the WO publication is found on page 6 in

the Summary of the Invention as a "...method of rapidly freezing and storing water or liquid samples without the use of cryoprotectants to minimize or eliminate damage from ice crystals or osmotic forces, allowing very high recovery rates on thawing." The WO publication teaches away from using a cryoprotectant to cryopreserve oocytes.

Applicants conclude that it is improper to combine U.S. Patent 5,780,295 with WO 99/66271 to argue unpatentability of the claimed invention because the WO publication specifically teaches away from use of cryoprotectants in practicing vitrification methods, particularly with oocytes.

Rejection of canceled claims 40-43 and 45 under 35 U.S.C. §103:

Canceled claims 40-43 and 45 were rejected under 35 U.S.C. §103(a) as unpatentable over US Patent No. 5,780,295 taken with Yang, *et al.*, Papis, *et al.*, and Martino, *et al.* As with previous rejections, the Action relied on the disclosed method of the '295 patent while admitting that oocytes and equilibrium solutions are not disclosed, including type and amount of protectant. The WO99/66271 application is cited for disclosing a method of rapid freezing through microdroplet contact with a cryogenic surface and further teaches that cryopreservation agents are conventionally added to biological materials to maximize cell survival. The Yang, *et al.* and Papis *et al.* references are asserted to demonstrate that optimization protocols for cryopreservation require multiple steps despite the methods disclosed that utilize such things as plastic straws rather than metals. Martino, *et al.* is cited as showing that metal grids could be used in place of straws in optimizing oocytes or embryos.

Applicants respectfully submit that the Action may have utilized hindsight and a "pick and choose" analysis of five separate references. Following the teaching of the '295 patent, the skilled practitioner would disregard the plastic straw method of Martino, *et al.* and would NOT be tempted to experiment with cryopreservatives because (1) the '295 patent is silent with regard to oocytes and only provides examples with other, quite different, cell types, and; (2) The WO application not only stresses the difficulties in oocyte preservation but also teaches away from using cryopreservation (as discussed above)